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European Network of Gynaecological Oncological Trial Groups' Requirements for Trials between Academic Groups and Industry Partners – a new Model D for drug and medical device development

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The European Network of Gynaecological Oncological Trial Groups (ENGOT) is a research network of the European Society of Gynaecological Oncology (ESGO), which was founded in 2007. Currently, 21 European trial groups are members of ENGOT (Appendix). As a network of European national or regional clinical trials groups, ENGOT has successfully conducted more than 70 European clinical trials in gynaecological malignancies. The majority of clinical studies performed via the ENGOT are randomized Phase III trials, which have led to drug approvals and change in the standard of care in gynaecological malignancies. At a meeting in 2013, the ENGOT Strategic Group decided to initiate working groups for early drug development, biobanking, translational research, and rare gynaecological cancer. Within the Horizon 2020 plan, a COST action was proposed by ENGOT and financed with the goal to promote networking in the field of rare gynaecological cancer. This action was named Gynocare (https://www.cost.eu/actions/CA18117/#tabs|Name:overview).

The goal of all these ENGOT working groups is to accelerate the development of new therapies, based on a solid scientific rationale, for women with gynaecological cancer through European collaboration, from concept to cure. For this purpose, we use the multidisciplinary expertise available within ENGOT and promote networking among expert centres belonging to different European countries. ENGOT also collaborates with groups outside the European Network,[1]. To achieve this goal, collaboration with industry partners is essential to quickly translate innovation into improved patient care.

The ENGOT groups' "Requirements for Trials between Academic Groups and Industry Partners" was published in the International Journal of Gynaecologic Cancer in 2010,[2]. These were re-evaluated and published in 2015 with the experience gained following the performance of several large randomised phase III trials,[3]. In these prior manuscripts, three Models of cooperation (Models A, B and C) are described, which have been successfully implemented during cooperation with industry partners and when developing hypothesis generating and practice changing phase II and phase III clinical trials. However the model of cooperation with industry now needs to be extended and adapted due to the complexity of the new research programmes that are required to achieve the goals mentioned above.

Based on this premise, we herein propose an additional model of cooperation with industry, Model D, that will help to establish more efficient ways of developing clinical trials in the evolving landscape of gynaecological cancer.

A number of situations require a new ENGOT Model D:

1) The development of new types of clinical trial design such as

- umbrella and basket trials in which different drugs/medical devices from different industry partners are tested in multiple arms as single agents or in drug combinations in one or more clinical indications.
- biomarker/pathway-driven trials in different tumour types with different drugs/medical devices from various industry partners tested over time within an adaptive model

2) The need for a more integrated framework to allow multi-industry cooperation with multiple academic groups within ENGOT within the same platform and if necessary with other groups outside ENGOT

3) The desire to create the opportunity to develop different drugs/medical devices over time within one platform to increase speed of development.

The objective of this manuscript is to describe the new Model D which incorporates the previous models and offers an opportunity for closer collaboration amongst multiple industry partners and multiple academic groups in early drug/medical device development.
This manuscript was discussed and approved by working group 4 (dedicated to bridging the gap between industry and biotechnology companies and translational research projects) and Action Chair of the Gynocare project and by the ENGOT Early Drug Development Network. It also underwent approval by the ENGOT Strategic Group and the ENGOT General Assembly prior to publication.

DESCRIPTION OF MODEL D

Model D allows the performance of several Phase I/II clinical trials with one or more industry partners and multiple ENGOT groups within an integrated programme.
In the following, we will refer to a programme as a research concept that requires Model D cooperation for early drug/medical device development (Figure 1).

When implementing Model D, a Memorandum of understanding (MoU) will be signed between industry partner(s) and ENGOT with the sole goal to document the willingness of cooperation on a specific programme. The legal framework will subsequently be included in the contracts of the specific trials between industry and the respective lead ENGOT group of each trial. The signed MoU will require a formal amendment if an additional company wishes to be included and to contribute to the programme. The residing ENGOT chair at the time of document completion will sign the MoU.
This MoU will specify in detail the following:

- introduction with the aims of the programme
- description of the unmet need in the area of the actual programme with details of underlying reasons that require cooperation within the new Model D
- definition of further procedures needed to implement the final programme and describe the governance and timeline of the programme
- description of the cooperation: the programme may involve multiple industry partners and multiple ENGOT academic groups
- definition of the intellectual property rights
- description of the clinical setting and the clinical trials within the programme
- maintenance of confidentiality

Once the MoU is signed, each clinical trial of the programme under the MoU will require separate contracts between the industry partner and the involved lead ENGOT group detailing all aspects including the roles and responsibilities. An alternative option is to execute one master contract between the industry partner and one ENGOT group and to additionally establish an intergroup agreements among all involved cooperating ENGOT groups.
These contracts will follow one of the previously described ENGOT Model,[2,3,4]. In case of trials involving drugs/medical devices from different industry partners contracts between industries may be needed.

Database property and Intellectual property (IP):

The Sponsor of each clinical trial has the ownership of the data within that trial.

The Sponsor can be an academic or cooperative group member (Model A or B) or an industry partner (Model C). In Model A, the database resides with, and is owned by the Lead ENGOT Group. In Model B, the database resides at a contract research organisation (CRO) but is owned by the Lead ENGOT Group (who is also the Sponsor). In Model C, the database resides at a CRO, and the CRO is contracted by the industry partner (Sponsor) or alternatively the database resides at the industry partner. The choice of a CRO is made in mutual agreement between ENGOT and the industry partner (where possible).

With respect to study drug/medical device inventions, the right to commercially develop the drug/medical device-related results of a trial remains the property of the industry partner both in industry and academically sponsored trials (as per contractual terms).

In the case of more than one industry partner being involved in the same clinical trial, each industry partner retains the IP of their own drug/medical device.

In the case of academically sponsored trials, the industry partner and the academic sponsor will negotiate a financial allocation for the complete transfer of the data for commercial purposes or filing at the timepoint of available results (as applicable). This procedure of negotiation will be part of the contract. The information regarding potential commercial use of the data will be included in the informed consent form (ICF).

Biomarker inventions related to the use of the study drug/medical device generated by the academic groups will be negotiated in the contract. All inventions not related to the use of the specific study drug/medical device and generated by the academic study groups may be the property of the academic groups in both academically and industry sponsored trials (e.g. translation research findings that might be patentable). Any shared IP arising from the programme will be negotiated in the contract.

Essential documents of Model D

For each programme, a template protocol, a template ICF for clinical trial participation and for sample acquisitions, a template eCRF (with common database elements) and (if applicable in industry-sponsored trial) a template translational sub-study protocol lead by ENGOT group with respective ICF, will be developed. The template protocol will include *mandatory* elements that are shared among the specific clinical trials within the programme (e.g. rationale of the programme, rationale of intervention, minimum set of in-/exclusion criteria, description of bio sampling, common statistical plan and endpoints, etc) and also *adaptive* elements. The mandatory elements of the template protocol must not be modified in the specific clinical trial protocol within the programme while the adaptive elements can be specific to each distinct clinical trial.

Common clauses will be developed that should preferably be used in the contracts between industry partner(s) and ENGOT academic group(s) for each clinical trial in the programme. Ideally a master contract can be drafted for each programme.

Principles of Model D Programmes

Timelines are of particular importance in early drug/medical device development with adaptability and flexibility being key enablers to speed. Model D programmes allow a high rate of adaptability e.g. by quickly adding a cohort (specific trial) into a basket trial programme if

sufficient data emerge to support expansion or by adding a new drug/medical device (specific trial) if new evidence supports its use in a particular patient population. ENGOT aims to build in high flexibility into Model D programmes to allow emerging data to be taken into consideration. Besides increased implementation of these key elements for early drug/medical device testing in Model D programmes, a major strength of ENGOT is efficacy in recruitment via the national academic groups. ENGOT has simultaneously conducted multiple randomised Phase III trials in similar indications by providing a large number of sites and avoiding overlapping trials at academic sites. A high number of experienced Phase I/II centres were identified within the ENGOT academic groups (ENGOT Early Drug Development Network). The organisation of early drug/medical device development via academic groups will allow avoidance of overlap at clinical sites in trials involving the same patient population within a programme, and will be particularly beneficial in Model D programmes involving multiple industry partners allowing allocation of different clinical sites to distinct trials. Furthermore, the organisation of ENGOT via academic groups has proven capability to successfully run clinical trials in rare gynaecological cancers.

Besides, ENGOT trials are based on scientific soundness and rigor, highest data quality and quality execution of trials according to Good Clinical Practice.

Translational Platform and Biobanking

Programmes performed according to Model D have a priority to promote translational research and biomarker discovery particularly in early drug development and rare gynaecological cancer. The translational activity does not have to be limited to the actual mechanism of action of the specific drug but should contribute to the better understanding of the disease. For biobanking, the use of the ENGOT biobank is strongly recommended and should be negotiated in the contract.

For industry sponsored clinical trials, a parallel academically led biobank together with a joint translational research plan should be considered. If this is not an option in an industry sponsored trial, a translational sub-study protocol, sponsored by an academic ENGOT group, and respective ICF can be developed. ENGOT academic groups should have priority in accessing residual biosamples held by industry partners in order to perform academic research. The ICF and contracts should include this possibility.

In the case of an academically sponsored trial, the biosamples will be collected, stored and managed under the responsibility of the ENGOT lead group. Any research project on collected biomaterials that is not pre-defined must be approved by the Scientific Board of the programme and conducted according to the national regulations of the patient enrolling countries in the programme.

Statistical considerations

Within the programme one common statistical plan should be considered and it is preferable to have at least one academic statistician involved. In addition, in each clinical trial within the programme, a second academic statistician may be involved. The entire database of the programme should be made available for later meta-analyses or subgroup analyses by the academic group or an intergroup consortium after approval of Sponsor and Programme Scientific Board,[2].

Committees

Each Programme will appoint a Programme Scientific Board that will be responsible for:

- coordination and harmonisation of the different clinical trials in the programme
- approving the template protocol, template eCRF, template ICFs, SAPs and common clauses of contracts
- checking implementation of common elements of essential documents in each clinical trial
- approving each clinical trial protocol
- approving the publication plan arising from the overall results and sub-studies of the programme (in distinction from results of each clinical trial)
- proposing and/or evaluating the need to amend the MoU

The Programme Scientific Board will appoint a Chair. The Programme Scientific Board will include at least one operational person and, if needed, experts in development and implementation of translational research or other relevant areas. Additional subcommittees (eg. Molecular diagnostic committee) can be appointed by the Programme`s Scientific Board, if needed. In Model D programmes consisting of Model C trials, the Programme Scientific Board will also have representatives of industry partner(s).

Each clinical trial within the Programme will appoint its own trial Steering Committee according to the general ENGOT rules. Responsibilities of the ENGOT Trial Steering Committee members are described earlier [2, 4]. The Chair of each trials Steering Committee will be a member of the Programme`s Scientific Board.

Publication rules

Model D will in general follow the rules for ENGOT publication (https://engot.esgo.org/discover/for-partners/).

In the case of a phase I/II trial within the Programme that has a substantial translational research component, separate rules compared to the general ENGOT publication rules (as pointed out above) apply when a manuscript is primarily concerned with the results of combined clinical endpoint (e.g. PFS) and a translational research endpoint. This might make it necessary to include authors not primarily affiliated to a group but contributing to laboratory work. In this case, rules must be agreed on in advance and presented to ENGOT at the time-point when the group applies for an ENGOT trial number.

The recommendation for defining authorship rules prospectively applies in particular for research projects in which the principal investigator of the clinical trial may neither get the first nor the senior position.

Overall, the publication authorship should consider both, the groups' contribution and translational laboratory activities. At minimum 51% of authorship positions should be distributed by the groups and reflect the general ENGOT publication rules.

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Appendix: ENGOT academic groups (alphabetically):

Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO-Study Group, Germany),
Austrian Arbeitsgemeinschaft für Gynäkologische Onkologie (AGO-Austria),
Belgian and Luxemburg Gynaecological Oncology Group (BGOG),
Cancer Trials Ireland (CTI)
Central and Eastern European Gynecologic Oncology Group (CEEGOG),
The Dutch Gynaecological Oncology Group (DGOG),
European Organisation for Research and Treatment of Cancer – Gynaecological Cancer Group (EORTC-GCG),
Grupo Español de Investigación en Cáncer de Ovario (GEICO),
Groupe d'Investigateurs Nationaux pour les Etudes des Cancers de l'Ovaire (GINECO),
Hellenic Cooperative Oncology Group (HECOG),
Israeli Society of Gynecologic Oncology (ISGO),
Mario Negri Gynecologic Oncology group (MaNGO),
Multicentre Italian Trials in Ovarian cancer and gynaecological malignancies group (MITO),
National Cancer Research Institute UK (NCRI),
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie (NOGGO),
Nordic Society of Gynaecological Oncology – Clinical Trial Unit (NSGO-CTU),
Polish Gynecologic Oncology Group (PGOG),
Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung (SAKK),
Scottish Gynaecological Clinical Trials Group (SGCTG),
Swiss GO Trial Group (Swiss GO),
Turkish Society of Gynaecologic Oncology (TRSGO).

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https://www.cost.eu/actions/CA18117/#tabs|Name:overview
Gynocare

European Network of Gynaecological Oncological Trial Groups' Requirements for Trials between Academic Groups and Industry Partners – a new Model D for drug and medical device development

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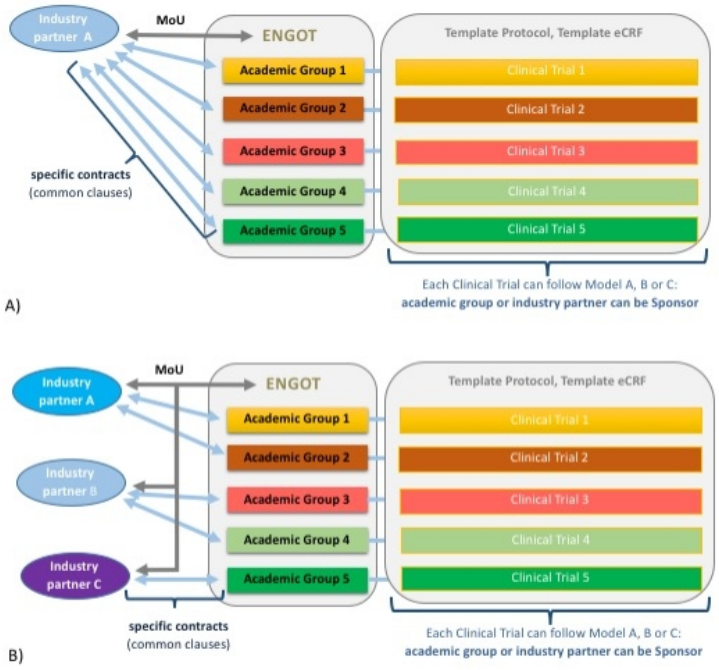

Figure 1: Example for a programme according to Model D.
Cooperation between A) one industry partner and multiple ENGOT academic groups, and B) several industry partners and multiple ENGOT academic groups is depicted.
In A) the example of specific contracts between the industry partner and each academic group is depicted. Alternatively, one mastercontract between the industry partner and one academic group can be executed and an additional intergroup agreement can be established among all participating academic groups in the programme. In case of cooperation with other groups outside ENGOT within a programme one or more clinical trials can e.g. be led by these other groups. The rules for ENGOT collaboration with other groups have been published previously,[1].
MoU: Memorandum of Understanding

338x360mm (54 x 54 DPI)